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THE IODINATION OF AZETIDINONE THIO COMPOUNDS

A CONVENIENT SYNTHESIS OF 3-IODO-3-METHYLCEPHAMS AND 3-ALKOXY-3-METHYLCEPHAMS

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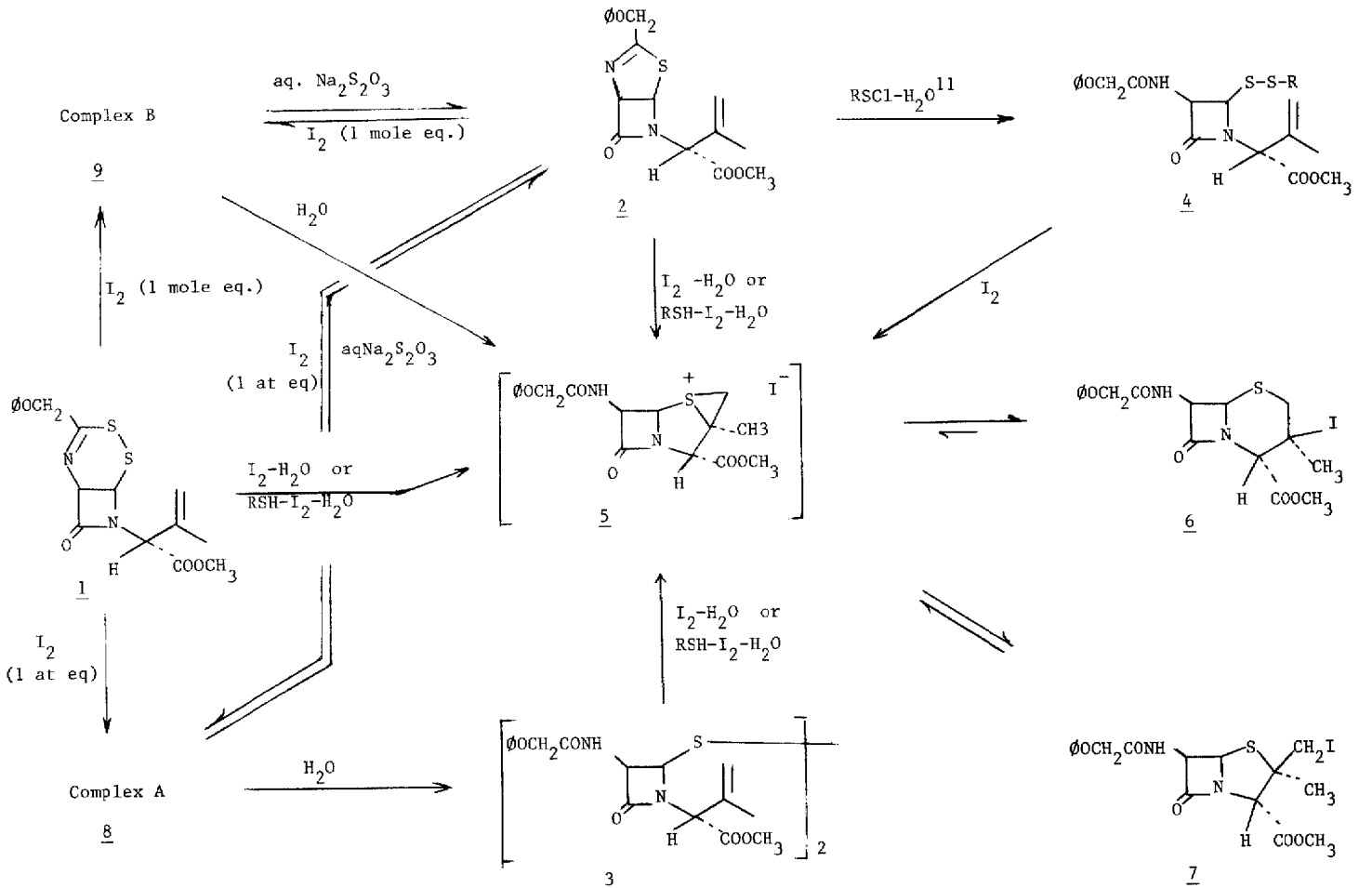
Although cephams substituted in the C_3-position and penams substituted in the C_2-methyl group by Cl, Br, OAc, ONO_2, and OH have been recently reported and studied [3,4], the corresponding iodo compounds have been neglected. The 3-iodocepham, 6, was made in high yields (over 80%) from the dithiazineazetidinones, 1, [5] or the thiazolineazetidinone, 2, [6] or the unsym-azetidinonedisulfide, 4 (R = 2-benzothiazole)[3], or the sym-azetidinonedisulfide, 3 [3,7], by reaction with iodine or sulfenyl iodides (as illustrated in the scheme). Various interconversions between these compounds using the same reagents were also possible.

Compounds 1 and 2 reacted with iodine in solvents such as toluene, dioxane, or methylene chloride to form complex A, 8, or B, 9, the stoichiometry of the reaction determining the nature of the complex. The nmr and ir spectra and tlc of these complexes were different from each other and from 1 or 2. The complexes were comparatively stable in the absence of moisture. On the addition of water, complex A (from the reaction with one atomic equivalent of iodine) gave high yields (over 80%) of the sym-azetidinonedisulfide, 3 [3,7,8], while complex B (from the reaction with one molar equivalent of iodine) gave the 3-iodocepham, 6, in about 30% yield. The conversion of 3 to 6 was achieved by repeating the reaction with iodine and water. The use of a sulfenyl iodide in place of iodine improved the conversion yields of 1, 2, and 3 to 6 from about 30% to over 80% in every instance. The sulfenyl iodide was conveniently generated *in situ* by the action of iodine on a mercaptan, a thioamide (including thiourea), a thioacid or a disulfide, the yield of 6 being dependent on the compound used. The best yields (about 85%) were obtained by using thiourea or 2-mercaptobenzothiazole. (Bromine and chlorine did *not* behave in the same way as iodine). Complex A or B on treatment with aqueous thiosulfate produced 2. The mechanism of these interesting reactions will be discussed in a later publication.

The 3-iodocepham, 6, after purification by column chromatography on silica gel, was obtained as a pale yellow foam which on heating became a glassy solid at 73 - 76°C and melted at 118-120°C. Its nmr ($CDCl_3$) spectrum δ7.85 - 6.92 (m, 6H, $C_6\underline{H}_5$ and $N\underline{H}$), 5.88 and 5.7 (dd, 1H, J = 4 c/s, C_7-$\underline{H}$), 5.42 (d, 1H, J = 4 c/s, C_6-$\underline{H}$), 4.95 (s, 1H, C_4-$\underline{H}$), 4.7 (s, 2H, -O-$C\underline{H}_2$-_, 3.85 (s, 3H, $COOC\underline{H}_3$), 2.98 (ABq, 2H, J = 15 c/s, C_2-$C\underline{H}_2$), 2.22 (s, 2H, C_3-$C\underline{H}_3$) was characteristic [10]. Small amounts of the 3-iodomethylpenam, 7, (about 5%) were detected in the nmr spectra of the crude products.


Complex B
9
aq. $Na_2S_2O_3$
I_2 (1 mole eq.)
H_2O
I_2 (1 mole eq.)
I_2 (1 at eq)
$aqNa_2S_2O_3$
I_2-H_2O or RSH-I_2-H_2O
1
I_2 (1 at eq)
Complex A
8
H_2O
2
I_2 -H_2O or RSH-I_2-H_2O
RSCl-H_2O 11
4
I_2
5
6
I_2-H_2O or RSH-I_2-H_2O
3
7

The unsym-azetidinone disulfide, 4 [3,11] (R = 2-benzothiazole) reacted readily with iodine (water was not necessary) in solvents such as CH_2Cl_2 or $CHCl_3$ to give quantitative yields of 6. The stoichiometry was not important in this instance. When an alcohol was used as solvent, reaction with iodine produced the 3-alkoxy-3-methylcepham. Thus with methanol as solvent, 4 gave a 60% yield of the 3-methoxy-3-methylcepham [12] after purification by chromatography. The nmr ($CDCl_3$) spectrum δ7.8 - 6.95 (m, 6H, $C_6\underline{H}_5$ and $N\underline{H}$), 5.85 and 5.68 (dd, 1H, J = 4 c/s, C_7-$\underline{H}$), 5.42 (d, 1H, J = 4 c/s, $C_6\underline{H}$), 4.63 (ss, 3H, C_4-$\underline{H}$ and -O-$C\underline{H}_2$-), 3.85 (s, 3H, $COC\underline{H}_3$), 3.32 (s, 3H, C_3-$OC\underline{H}_3$), 3.43 and 2.70 (ABq, 2H, J = 14 c/s, C_2-$C\underline{H}_2$), 1.22 (s, 3H, C_3-$C\underline{H}_3$) is characteristic of this compound.

Compound 6 undergoes ready dehydroiodination to produce the desacetoxycephalosporin in high yields (see Ref. 3 for similar dehydrobromination of the 3-bromo-3-methylcephams). Thus in neat pyridine at room temperature complete conversion to the ceph-3-em system occurs in 1.5 hrs. In a solvent such as benzene heating is necessary to bring about dehydroiodination, the time for complete reaction depending on the amount of pyridine used. In these dehydroiodinations employing pyridine, there is no evidence of the possible ceph-2-em in the nmr spectra of the crude products. When however stronger bases such as diisopropylethylamine, DBU or DBN are used both the ceph-2-em and ceph-3-em isomers are present in the product.

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